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ORIGINAL PAPER

Treatment results of Para-Testicular Rhabdomyosarcoma (PT-RMS) using radiation as an alternative to retro-peritoneal nodal dissection: A single Institution experience

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Summary *Background: Para-testicular Rhabdomyosarcoma (PT-RMS) has a favorable treatment outcome adopting multidisciplinary management; resection, namely high inguinal orchiectomy ± retro-peritoneal lymph node dissection (RPLND) followed by standard or intensive chemotherapy ± adjuvant radiation therapy.*
Patients and methods: This is a retrospective study including all patients with pathologically proven PT-RMS, presented to the National Cancer Institute, Cairo University, during the period from 2005 to 2020. Endpoints included overall survival, disease free survival and patterns of failure of different treatment modalities.
Results: Forty one patients were identified. Median age in our cohort was 15 years (range: 2-54 years). After a median follow up of 26 months (range, 3-75 months) ,two and five years OS were 100% and 91.7% respectively and median survival was not reached. Patients who underwent retro-peritoneal nodal dissection had a 5-year DFS rate of 100% versus 73% for those who received radiation to para-aortic nodes (p = 0.185). Limitations include retrospective nature and deviation from COG protocol.
Conclusions: This study shows promising results suggesting that less aggressive local treatment modalities including radiation to para-aortic chain could be an option in PT-RMS, given the excellent results of this subtype. However further validation in a prospective study is warranted.

KEY WORDS: *Para-testicular rhabdomyosarcoma; Retro-peritoneal dissection; Radiation therapy.*

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INTRODUCTION

Paratesticular rhabdomyosarcoma (PT-RMS) is a special entity of rhabdomyosarcoma with an estimated incidence around 7% of all patients with RMS (1).
The prognosis for patients with localized disease is excellent, owing to early detection of the tumor given its special location and a predominance of paired box gene (PAX)-fusion negative RMS (2, 3). This allows for using less aggressive local treatment modalities especially with the recent multiagent chemotherapy protocols and high sensitivity of imaging techniques.
Management strategy includes high inguinal orchiectomy with or without retro-peritoneal nodal dissection and multiagent chemotherapy depending on the stage and group of disease (4). Patients with no sampling of para-aortic nodes are managed as stage III disease. In our institute, retro-peritoneal nodal sampling is not widely adopted and radiation therapy to para-aortic chain is used as an alternative. Herein, we review our experience and clinico-epidemiological factors were studied as well as treatment strategies potentially influencing *disease-free survival* (DFS) in addition to *overall survival* (OS) and *loco regional recurrence* (LRR).we aim to explore treatment outcomes with radiation therapy instead of retro-peritoneal nodal dissection.

PATIENTS AND METHODS

This is a retrospective study involving all patients with para-testicular RMS presented to NCI, Cairo University in the period from 2005 till 2020.
IRB approval was obtained before data collection from ethical committee of *Faculty of Medicine, Cairo University*. No consents were required given the retrospective nature of the study.
Patients' records were reviewed to extract clinico-epidemiological data including age, pathological subtype, tumor size , risk stratification, staging and treatment data including type of surgery (biopsy or resection, para-aortic lymph node dissection), chemotherapy regimen and radiotherapy details (dose, overall period of treatment, radiation technique and timing of radiation),and patterns of failure. Patients with incomplete treatment records were excluded from data analysis.
All patients were diagnosed by initial biopsy (high inguinal orchiectomy or trans-scrotal). Patients who underwent complete surgical staging were staged according to *IRSG Postsurgical Grouping Classification* (5) (Table 1), while those who underwent orchiectomy only without nodal assessment or those with clinical positive nodes were managed as

Table 1.
IRSG Postsurgical Grouping Classification.

Group 1	Localized disease, completely resected, no microscopic residual
A	Confined to site of origin, completely resected
B	Extends beyond site of origin, completely resected
Group 2	Gross total resection
A	Residual microscopic disease (positive margins)
B	Involved regional nodes, completely resected
C	Microscopic local and/or regional residual disease
Group 3	Incomplete resection or biopsy with gross residual
Group 4	Distant metastasis

group III. Pretreatment clinical staging was per IRSG pre-surgical staging (5) (Table 2). Work up included scrotal U/S, MRI of the pelvis, CT of chest and abdomen with contrast and bone scan. PET-CT was done for 5 patients for initial staging and/or post chemotherapy to assess the treatment response in last two years (2019-2020).
Lymph node evaluation was done using staging CT of the abdomen and pelvis in all cases. Surgical nodal staging was done in only 4 cases.

Treatment details

All patients underwent surgery for the primary testicular tumor (most of them were by inguinal approach); only 4 patients underwent therapeutic *retroperitoneal lymph node dissection* (RPLND) for grossly enlarged nodes on CT. Postoperative chemotherapy was used according to the Intergroup Rhabdomyosarcoma Study IRS- IV chemotherapy protocol (vincristine, dactinomycin, and cyclophosphamide) (6) for 42 weeks. A flow chart of the protocol is provided in Figure 1.
Hemi-scrotum irradiation was used in cases of scrotal violation (trans-scrotal approach).
Iliac and inguinal nodal radiation was used with para-aortic nodal radiation in cases of presence of clinically involved nodes in these stations.
Regarding radiation therapy planning, patients were fixed with a mattress during CT simulation. CT cuts were taken with a slice thickness of 3 mm from level of suprasternal notch down to mid-thighs. A three-dimensional conformal radiotherapy technique was commonly used for treatment.

Figure 1.
Diagrammatic scheme of IRS-IV protocol.

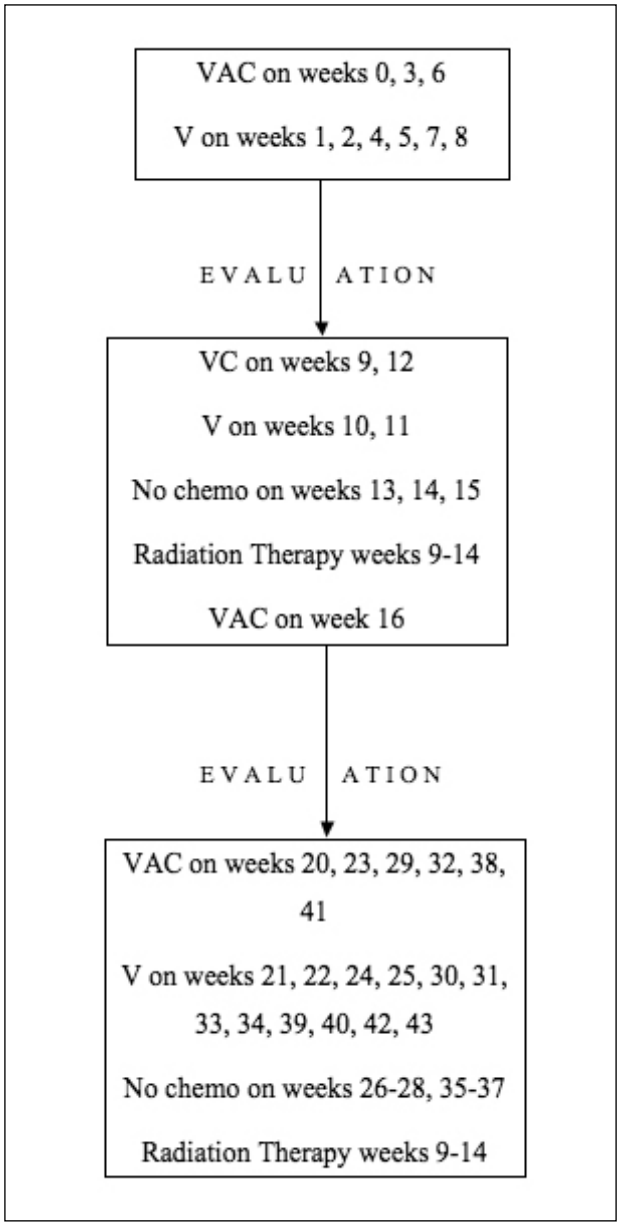


Table 2.
IRSG Pre-surgical Staging Classification.

Stage	Sites	Tumor (T)	Size	Node (N)	Metastases (M)
I	Orbit, head and neck (excluding PM), GU: non-bladder/non-prostate	T_1 or T_2	a or b	N_0, N_1 or N_x	M_0
II	Bladder/prostate, extremity, cranial, PM other (includes trunk, retroperitoneum, and so on)	T_1 or T_2	a	N_0 or N_x	M_0
III	Bladder/prostate, extremity, cranial, PM, other (includes trunk, retroperitoneum, and so on)	T_1 or T_2	a b	N1 N_0, N_1 or N_x	M_0
IV	All	Any	Any	Any	M_1

Tumor: T_1, confined to anatomic site of origin, (a) < 5 cm in diameter, (b) > 5 cm in diameter; T_2, extension and/or fixative to surrounding tissue, (a) < 5 cm in diameter, (b) > 5 cm in diameter; regional nodes: N_0, regional nodes clinically negative; N_1, regional nodes clinicallypositive; N_x, clinical status is unknown; metastasis: M_0, no distant metastasis; M_1, metastasis present. GU, genitourinary; PM, para-meningeal.

Starting from year 2020, *Intensity-Modulated Radiation Therapy* (IMRT) technique was used for better sparing of organs at risk. Radiotherapy doses were dependent on the completeness of surgical resection of the primary tumor (*Clinical Group*) and presence or absence of involved regional lymph nodes. After resection, patients with complete resection and stage I alveolar histology were treated to 36 Gy, those with stage II and uninvolved nodes received 41.4 Gy, those with pathologically involved nodes received 41.4 Gy and patients with positive gross nodes in planning CT received 50.4

Gy. The *gross tumor volume* (GTV) was defined as any gross nodal disease on planning CT or post-chemotherapy PET-CT. The *clinical target volume* (CTV) was defined as 1.5 cm expansion on aorta and *inferior vena cava* (IVC) from level of *11th dorsal vertebra* (DV11) down to bifurcation, excluding bowel, bone and muscles. The *planning target volume* (PTV) was defined as an additional 1 cm margin to CTV.
Kidneys, bowel and spinal cord were delineated as organs at risk. PTV coverage of minimum 95% of dose to 95% of volume was required for plan acceptance. D_{max} of cord was limited to < 45 Gy and bilateral kidney V24 was limited to < 50%.
Radiation therapy was started at week 13 in patients with Low Risk (14 patients) whereas in other cases it was usually given at week 20 as per protocol.

Statistical analysis

Data was analyzed using IBM SPSS advanced statistics (*Statistical Package for Social Sciences*), version 21 (*SPSS Inc., Chicago, IL*).
Numerical data was described as mean and standard deviation or median and range as appropriate, while qualitative data were described as number and percentage.
Endpoints were the disease-free survival, metastasis-free survival, loco-regional control and overall survival. Overall survival was defined as the time from primary diagnosis date to death (all-cause). Time to loco-regional recurrence was defined as time from primary treatment to recurrence at the primary tumor site or regional lymph nodes, whichever comes first; distant recurrences and deaths that occur before local events were ignored. Distant recurrence was defined as recurrences outside these loco-regional sites; deaths and loco-regional recurrences that occur before distant events were ignored. *Disease-free survival* (DFS) was defined as the time from primary treatment to loco-regional recurrence, distant recurrence, whichever comes first.
Comparisons between the two groups were made using either Chi- square test or Fishers exact test for categorical data. For quantitative data comparison between 2 groups was done using either parametric or non-parametric t-test as appropriate.
Survival analysis was done using Kaplan-Meier method and comparison between survival curves was done using Log rank test. A p-value less than 0.05 was considered statistically significant. All tests were two tailed.

Results

Forty one patients with pathologically proven PT RMS were identified in the period from January 2005 till December 2020.
The Median age in our cohort was 15 years (range: 2-54 years). Children below 10 years constituted 24% of the total population. Thirty seven (90%) patients had embryonal histology. Retroperitoneal lymph node involvement was present in twelve (29%) patients by CT evaluation (four patients < 10 years and eight patients > 10 years). Ten patients presented with initially metastatic disease (eight patients to lungs and two patients to supra-clavicular lymph nodes). Demographic and pathological characteristics of the patients are summarized in Table 3.

Table 3.
Demographic and pathological characteristics of patients in this study.

	N = 41 (%)
Age	
Median (range)	15 (2-54)
≤ 10	10 (24)
> 10	31 (76)
Histological type	
Alveolar	2 (4.9)
Embryonal	37 (90.2)
Pleomorphic	2 (4.9)
Staging	
Stage 1	23 (56.1)
Stage 2	4 (9.8)
Stage 3	4 (9.8)
Stage 4	10 (24.4)
Grouping	
Group 1	8 (19.5)
Group 2	13 (31.7)
Group 3	20 (48.8)
Risk stratification	
Low risk	14 (34.1)
Intermediate risk	14 (34.1)
High risk	13 (31.7)

Treatment related characteristics

Thirty-nine (95%) patients were surgically excised completely by high inguinal orchiectomy and high cord ligation at the internal ring prior to tumor mobilization as per international guidelines; only 2 patients (5%) were managed by trans-scrotal approach.
Thirty seven (90%) patients did not undergo *retroperitoneal lymph node dissection* (RPLND), while four (10%) patients underwent inguinal orchiectomy with RPLND (all were > 10 years),
Patients were treated according to *Intergroup Rhabdomyosarcoma Study* IRS-IV protocol. All patients were treated by systemic chemotherapy (VAC based regimens) for 42 weeks.
Radiotherapy was adopted for local control in thirty one (75%) patients, while 8 patients did not receive radiotherapy as they were low risk group (stage I, group I, embryonal histology). One patient did not receive radiation due to his guardian's refusal and one patient did not receive local treatment due to progression during chemotherapy and he was shifted to second line chemotherapy *Ifosfamide/Carboplatin/Etoposide* (ICE), with good response. Patients who received radiation to scrotum were due to scrotal violation during surgery and those who received radiation to inguinal and ipsilateral iliac nodes was due to presence of gross disease at these sites at presentation.
The timing of radiotherapy in COG Protocol was in week 13 in all risk groups. Patients in low risk group received radiotherapy at week 12 and some patients were delayed to week 20. The median radiotherapy dose was 36Gy

Table 4.
Treatment related characteristics in this study.

Surgical approach n = 41 (%)	
Inguinal	39 (95)
Scrotal	2 (5)
PALN dissection	
Yes	4 (10)
No	37 (90)
PALN status	
Positive	12 (29)
Negative	29 (71)
Type of CTH	
VAC	32 (78)
VAC-ICE	6 (15)
VAC-ICE-IE	1 (2.4)
VCR	2 (5)

(range, 19.5- 50.4 Gy). Treatment related characteristics are summarized in Table 4.

Figure 2.
KM curve representing overall survival for the whole study group.

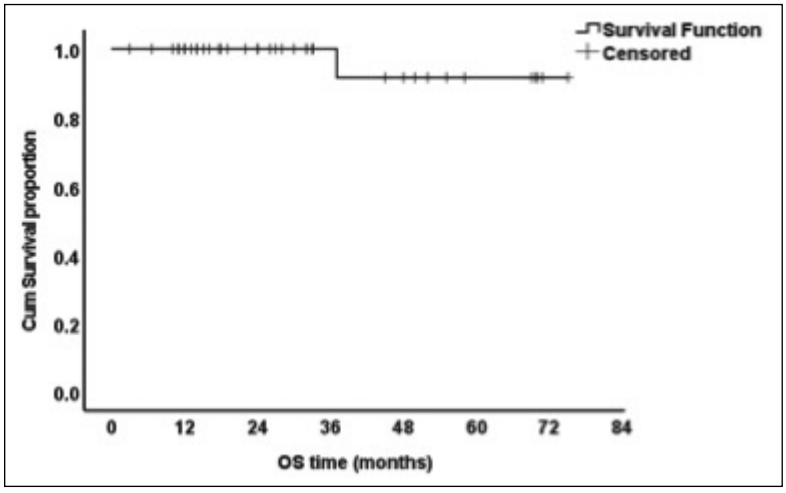
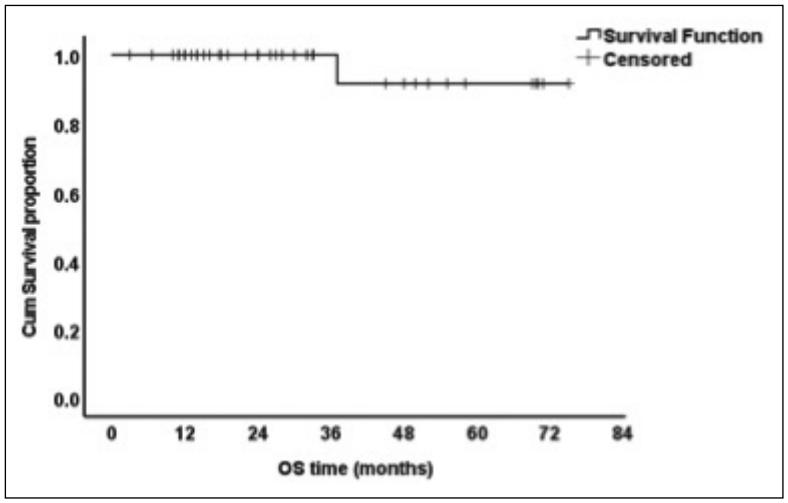


Figure 3.
Kaplan Meier curve representing DFS for the whole study group.



Patterns of failure

One patient had distant failure in lung, one patient had distant failure in bones and seven patients had nodal failure, three of them in ilio-inguinal nodes and 4 patients had para-aortic failure. In patients who underwent RPLND, one patient had para-aortic failure.

Survival analysis

Overall survival (OS)

After a median follow up of 26 months (range, 3-75 months), two and five years OS were 100% and 91.7% respectively and median survival was not reached (Figure 2).

Five year survival rate for patients < 10 years were 100% versus 86% for patients above 10 years of age (p = 0.390).

Disease Free Survival (DFS)

Five years disease free survival for the whole group was 77 percent (Figure 3). Patients who underwent retro-peritoneal nodal dissection had a 5-year DFS rate of 100% *versus* 73% for those who received radiation to para-aortic nodes (p = 0.185).

Five years DFS was 100% for patients < 10 years *versus* 71% for those > 10 years (p = 0.106). No difference in DFS between patients who had positive para-aortic nodes at presentation (n = 12) and those with negative para-aortic nodes (n = 29), with a 5-year DFS rate 90 percent *vs.* 72 percent, respectively (p = 0.287).

Local control (LC)

The one-year LC is 85% for whole study group while the five-year LC is 71.2%. No difference in LC between patients with positive para-aortic nodes at presentation and those with negative nodes at 5 years (89 percent *vs.* 60 percent, respectively, p = 0.158).

Discussion

This retrospective study included 41 patients with *para-testicular Rhabdomyosarcoma* (PT RMS) who presented to *NCI - Cairo University* in the period from 2005 to 2020.

The median age of the study patients group was 15 years which is comparable to other studies showing a median age of 16.5 years (7).

The embryonal pathological subtype constituted 90% of the study group. Similar results were reported in the literature with predominance of the embryonal histology representing 70% (7).

Regarding the surgical and clinical group, the majority of the studied patients were categorized as Group 3 (50%) which is consistent with the analysis of PT RMS patients treated in IRS II through IV in which surgical group 3 was reported in (40%) of cases (7).

Regarding the IRSG stage, 56% of studied patients presented in stage I while 25% of

patients had stage IV disease. Findings are in agreement with other studies which reported stage I and IV diseases in 40% and 40% of cases respectively (7).

Approximately 29% of patients with PT-RMS presented with retroperitoneal lymph node disease which is comparable to another study in which approximately 25% of patients with PT-RMS had Positive retroperitoneal lymph node disease (6).

The treatment of the patients in this study followed the international guidelines regarding the surgical approach for the primary tumor (high inguinal orchiectomy) which was followed by standard chemotherapy protocol. As for the nodal regional control in positive retroperitoneal lymph nodes, radiotherapy was used in most of the patients (90%) instead of RPLND which was only done in four patients (10%). This policy adapted by our institute is contradictory to the current protocol for *Children's Oncology Group* (COG) adapting ipsilateral staging RPLND for all boys aged 10 years or more and for those with enlarged lymph nodes suspicious for metastatic disease on CT scan, or patients with alveolar histology irrespective of the age (8). Retro-peritoneal nodal dissection carries a high post-operative morbidity rates between 5-20% at high-volume centers. The most common complications being small bowel obstruction, retrograde ejaculation, lower extremity lymphedema, hydronephrosis and chylous ascites (9-11). These complications are considered more significant compared for nodal irradiation complications which include radiation dermatitis, gastroenteritis, and myelosuppresion (12).

Despite these low rates of para-aortic nodal dissection in our study, median OS was not reached and the calculated one and five year OS rates were 100% and 91.7% respectively, reflecting the excellent prognosis of the disease regardless of the nodal regional treatment modality used. These results are comparable to similar studies which reported overall survival rates ranging between 81 and 95 percent (6, 13, 14).

The retroperitoneal lymph node positivity at presentation (whether clinical or pathological) did not influence the outcome as there was no difference in treatment related outcomes between patients with positive and negative para-aortic nodes at presentation, reflecting the excellent outcome despite less intensive treatment in our study.

In terms of DFS, 5-year DFS rate was 73% in patients who received radiotherapy to para-aortic chain *versus* 100% for those who underwent retro-peritoneal nodal dissection with no significant difference between both groups statistically ($p = 0.185$). Only one patient (2.7%) out of 37 patients in our study experienced isolated regional failure in para-aortic chain.

This is comparable to another study which was held by SIOP 2016 which reported 5-year DFS 83% in patients who underwent Radical inguinal orchiectomy without RPLND (15).

In summary, our study shows a favorable outcome in PT-RMS patients managed with radiation to para-aortic chain instead of surgery. This might be attributed to the indolent nature of the disease itself or the efficacy of radiation. However, a prospective study may be warranted. To our knowledge, this is the first work addressing radiation as an alternative to surgery in PT-RMS.

Limitations of this study include its retrospective nature which makes it subjected to selection bias, small sample size, lack of toxicity scoring and *quality of life* (QoL) assessment of the patients, lack of PET-CT staging which might have underestimated the real incidence of clinically positive retro-peritoneal nodes and deviation from the current COG protocol. However in such rare diagnosis where prospective trials are difficult to conduct, institutional series remain instructive.

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Conflict of interest: The authors declare no potential conflict of interest.